Plecanatide for Treating Chronic Idiopathic Constipation: A Pooled Analysis of Efficacy and Safety

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Background

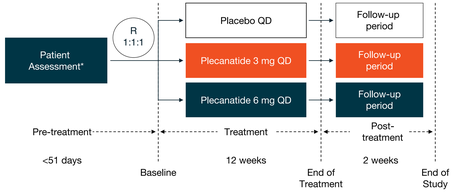
- Chronic idiopathic constipation (CIC) is a common gastrointestinal disorder, affecting ~14% of the population.[1,2]
- CIC symptoms are heterogeneous and can negatively impact health-related quality of life, productivity, and healthcare costs.[3-7]
- Treatment of constipation may be challenging as many patients cited dissatisfaction with their treatments[3]; therefore, additional treatment options for CIC may benefit patients.
- Plecanatide is structurally identical to human uroguanylin (with the exception of a single amino acid substitution), and preclinical evidence suggests that plecanatide replicates the pH-sensitive binding of uroguanylin to and activation of guanylate cyclase-C receptors, acting primarily in the small intestine coinciding with physiological areas of fluid secretion and contributing to normal bowel function.
- Plecanatide has been studied in the two largest phase 3 clinical trials conducted to date (*ClinicalTrials.gov* identifiers: NCT01982240; NCT0212247) and is approved in the United States as a once daily oral tablet for the treatment of adults with CIC.

Objective

- To evaluate the efficacy and safety of plecanatide in adult patients with CIC through a pooled analysis of two identically designed phase 3 trials, including the impact on patient-reported secondary outcomes.

Methods

Figure 1. Study Design for the Phase 3 Studies



*Electronic diary assessment for eligibility, compliance, and baseline parameters was completed during the last 2 weeks of the pre-treatment period. R=randomization; QD=once daily.

- Two 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 clinical studies were conducted to assess oral plecanatide (3 mg and 6 mg once daily) for the treatment of adults with CIC (**Figure 1**).
- Eligible patients for the study included:
  - Males or females (not pregnant or lactating), aged 18–80 years (inclusive)
  - Patients who met the Rome III functional constipation criteria as modified for this study
  - Patients who met the modified Rome III criteria also had to demonstrate the following during the 2-week pretreatment diary assessment:
    - <3 complete spontaneous bowel movements (BMs) each week
    - Bristol Stool Form Scale (BSFS) score of 6 or 7 in <25% of spontaneous BMs
    - ≥1 of the following:
      - BSFS score of 1 or 2 in ≥25% of BMs
      - A straining value recorded on ≥25% of days when a BM was reported
      - ≥25% of BMs resulted in a sense of incomplete evacuation
- Efficacy analyses were based on the intention-to-treat population.
- The primary efficacy endpoint was the percentage of durable overall complete spontaneous bowel movement (CSBM) responders, defined as patients who were weekly CSBM responders for ≥9 of the 12 treatment weeks, including ≥3 of the last 4 weeks of treatment.
  - A weekly CSBM responder was defined as a patient who had ≥3 CSBMs per week and an increase from baseline of ≥1 CSBM for that week.
- Secondary efficacy endpoints included the mean change from baseline in the frequency of spontaneous bowel movements (SBMs) and CSBMs, and the severity of patient-reported symptoms of straining, abdominal bloating, and abdominal discomfort.
  - Symptom severity was rated at its worst on a 5-point scale of 0–4, where 0=none and 4=very severe.
- Safety and tolerability were assessed by the incidence, nature, and severity of treatment-emergent adverse events (TEAEs).

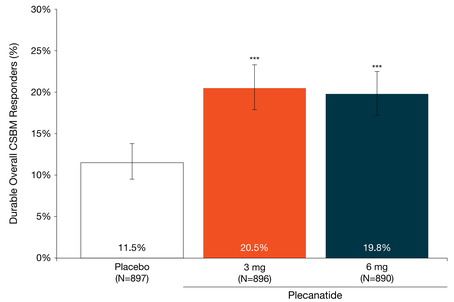
Results

Table 1. Demographics and Baseline Characteristics

	Placebo (N=897)	Plecanatide 3 mg (N=896)	Plecanatide 6 mg (N=890)
Age, years, mean (range)	45.5 (18–80)	45.2 (18–80)	45.2 (18–80)
Females, %	78.8%	79.6%	80.3%
Race, %			
White	72.9%	71.8%	70.3%
Black	22.2%	24.2%	23.6%
Other	4.9%	3.9%	6.1%
Weight, kg, mean (range)	76.7 (40.9–135.6)	77.6 (41.3–147.0)	77.7 (45.0–126.6)
BMI, kg/m^2, mean (range)	28.02 (17.8–41.7)	28.35 (18.2–39.9)	28.37 (18.1–40.0)

- There were 2683 patients in the combined ITT population, of which 798 placebo-treated patients and 1567 plecanatide-treated patients (3 mg, n=784; 6 mg, n=783) completed treatment.
- Demographics, which included a high percentage of males (~20%), and baseline characteristics were similar across treatment groups (**Table 1**).

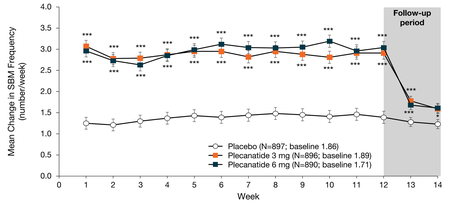
Figure 2. Percentage of Durable Overall CSBM Responders



***P<0.001 vs placebo. Values are percentage ± 95% confidence interval.

- A significantly greater percentage of patients in each plecanatide group were durable overall CSBM responders compared with placebo (**Figure 2**).

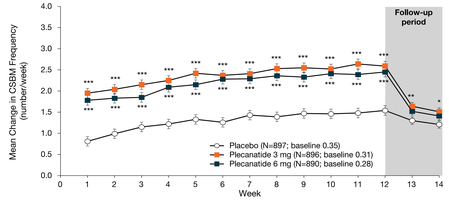
Figure 3. Change From Baseline in Weekly SBM Frequency by Time Point



***P<0.001, *P<0.05 vs placebo. Values are least squares mean change from baseline ± standard error.

- Improvements in the weekly frequency of SBMs were significantly greater for plecanatide-treated patients compared with placebo-treated patients, beginning after the first week of treatment and maintained through week 12 (**Figure 3**).

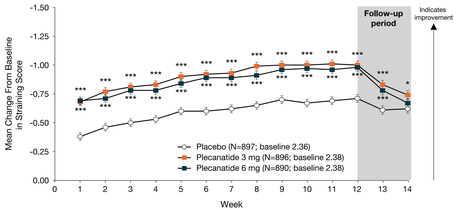
Figure 4. Change From Baseline in Weekly CSBM Frequency by Time Point



***P<0.001, **P<0.01, *P<0.05 vs placebo. Values are least squares mean change from baseline ± standard error.

- Improvements in the weekly frequency of CSBMs, an SBM with the sensation of complete evacuation, were significantly greater for plecanatide-treated patients compared with placebo-treated patients, beginning after the first week of treatment and maintained through week 12 (**Figure 4**).

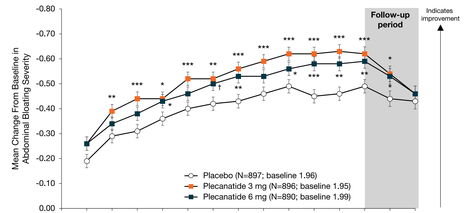
Figure 5. Change From Baseline in Straining Score by Time Point



***P<0.001, *P<0.05 vs placebo. Values are least squares mean change from baseline ± standard error.

- Statistically significant improvements in straining severity were demonstrated with plecanatide 3 mg and 6 mg compared with placebo, beginning after the first week of treatment and maintained through week 12 (**Figure 5**).

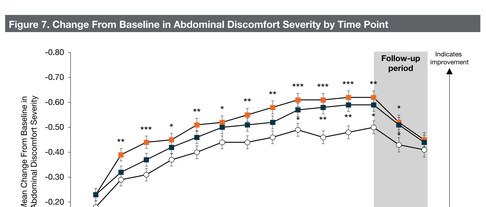
Figure 6. Change From Baseline in Abdominal Bloating Severity by Time Point



***P<0.001, **P<0.01, *P<0.05, †P=0.05 vs placebo. Values are least squares mean change from baseline ± standard error.

- Significant improvements in abdominal bloating severity were demonstrated for plecanatide 3 mg and 6 mg compared with placebo, with significant differences for plecanatide 3 mg observed after week 2 and maintained through week 12 (**Figure 6**).

Figure 7. Change From Baseline in Abdominal Discomfort Severity by Time Point



***P<0.001, **P<0.01, *P<0.05 vs placebo. Values are least squares mean change from baseline ± standard error.

- Significant improvements in abdominal discomfort severity were demonstrated for plecanatide 3 mg and 6 mg compared with placebo, with significant differences for plecanatide 3 mg observed beginning at week 2 and maintained through week 12 (**Figure 7**).

Table 2. Summary of Treatment-Emergent Adverse Events (TEAEs)

Patients, n (%)	Placebo (N=924)	Plecanatide 3 mg (N=941)	Plecanatide 6 mg (N=926)
≥1 TEAE*	265 (28.7%)	288 (30.6%)	288 (31.1%)
Diarrhea	12 (1.3%)	43 (4.6%)	47 (5.1%)
Nasopharyngitis	14 (1.5%)	11 (1.2%)	20 (2.2%)
≥1 Serious Adverse Event†	12 (1.3%)	14 (1.5%)	9 (1.0%)
≥1 TEAE leading to discontinuation	20 (2.2%)	39 (4.1%)	42 (4.5%)
Diarrhea	4 (0.4%)	18 (1.9%)	17 (1.8%)

*TEAEs occurring in ≥2% of patients in any treatment group.
†SAEs include 6 pregnancies (which were to be coded as SAEs per the protocol). Pregnancies were reported in 2 placebo patients, 3 plecanatide 3 mg patients, and 1 plecanatide 6 mg patient; therefore, the adjusted SAE rates are 1.1% (n=10), 1.2% (n=11), and 0.9% (n=8), respectively.

- Both plecanatide doses were safe and well tolerated, with a low incidence of diarrhea and discontinuation due to diarrhea (**Table 2**).

Discussion

- **Pooled results from the 2 largest double-blind studies in adult patients with CIC demonstrated that, relative to placebo, plecanatide treatment resulted in significantly greater percentages of durable overall CSBM responders, an endpoint intended to demonstrate the lack of therapeutic tachyphylaxis.**
- **Both plecanatide doses significantly increased the frequency of bowel movements and decreased the severity of straining beginning the first week of treatment, with significant improvements maintained throughout the 12 weeks of treatment.**
- **Both plecanatide doses significantly improved abdominal bloating and discomfort, with significant differences vs placebo observed from week 2 to week 12 of treatment.**
- **In the 2-week post-treatment follow-up period, the pharmacodynamic effect of plecanatide on stool frequency, straining, and abdominal symptoms diminished, and the symptom assessments merged with those of the placebo group.**
- **TEAEs resulted in study discontinuation of ~4% of plecanatide-treated patients compared to ~2% of placebo-treated patients.**
- **Diarrhea, the most common TEAE experienced and an important side effect for CIC treatment, was experienced by ~5% of plecanatide-treated patients compared to ~1% of placebo-treated patients.**
- **In conclusion, plecanatide treatment significantly improved symptoms commonly associated with CIC, demonstrating a significant therapeutic effect within the first (stool frequency and straining) or second week (abdominal bloating and discomfort) and lasting through the end of treatment and with a low incidence of adverse events, including diarrhea.**

References

1. Higgins PD, Johanson JF. *Am J Gastroenterol*. 2004;99:750–9.
2. Suares NC, Ford AC. *Am J Gastroenterol*. 2011;106:1582–91.
3. Johanson JF, Kralstein J. *Aliment Pharmacol Ther*. 2007;25:599–608.
4. Flourie B, Not D, Francois C, Prost a la Denise M. *Eur J Gastroenterol Hepatol*. 2016;28:525-31.
5. Heidelbaugh JJ, Stelwagon M, Miller SA, Shea EP, Chey WD. *Am J Gastroenterol*. 2015;110:580-7.
6. Irvine EJ, Ferrazzi S, Pare P, Thompson WG, Rance L. *Am J Gastroenterol*. 2002;97:1986-93.
7. Nellesen D, Yee K, Chawla A, Lewis BE, Carson RT. *J Manag Care Pharm*. 2013;19:755-64.

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Disclosures

M Hixson is an employee and stockholder of Synergy Pharmaceuticals Inc. SCC Rao declares no conflicts of interest.